Amendments to the Specification

Applicants have amended the Specification to include the correct chemical name of the compound DPI as diphenylene iodonium.

Amendments to Claims

Applicants have amended independent Claim 1 and dependent Claims 9-12 to more accurately recite the subject matter of the present invention. Applicants submit that these amendments do not change the scope of the claims at issue but rather merely clarify the subject matter recited therein.

Claims 1 and 8-13 are Fully Enabled by the Specification

The PTO has rejected Claims 1 and 8-13 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not fully enabled by the Specification. Specifically, the Examiner believes that there is insufficient evidence that the claimed method would function "for activating cytotoxic lymphocytes or for protecting cytotoxic lymphocytes after administering DPI to a patient". The Examiner required demonstration that NK cells are activated by DPI.

The Applicants respectfully points out that Examples 2 and 3 describe the effects of DPI on MO-induced inhibition of stimulated lymphocytes (pages 26-28). In Example 2, both histamine and DPI protect the CTLs activated by IL-2 from inhibition by MO, as well as activate the IL-2-stimulated CTLs already inhibited by MO. This activating and protecting effect is measured by increased CD69 expression on T-cells and percentage of apoptotic T-cells respectively (Example 2, Figure 1). It is well known in the art that the CD69 group of antibodies recognizes activated T-cells and other activated immune cells (page 25, lines 8-9). Thus, Figure 1 unequivocally demonstrates that DPI significantly increased the CD69 expression on T-cells (left panel) over IL-2 alone in the presence of MO, proving that DPI activates MO-inhibited T-cells stimulated by IL-2. The right panel of Figure 1 demonstrates that DPI protects T-cells from apoptosis in the presence of MO independent from IL-2.

The Examiner also believes that that the *in vivo* methods of treatment lack support due to their high unpredictability. The Applicants assert that because the experiments described in Examples 1 and 2 were performed in donor blood, the obtained results can be used by a skilled artisan as an adequate indicator of the effects of the tested compounds in the bloodstream, i.e. *in vivo*.

The Examiner also believes that Claim 13 is not supported as "no specific assay of the inhibition of hydrogen peroxide production is disclosed". However, it is well known in the art that the synergistic enhancement of NK cell cytotoxicity by combined histamine and IL-2 treatment in the presence of MO results from suppression of an inhibitory signal generated by MO. Said inhibitory signal is a result of generation of reactive oxygen metabolites such as hydrogen peroxide by the MO (page 5, lines 30-31 and page 6, lines 1-5). Accordingly, the present application provides sufficient teachings with which to assay hydrogen peroxide production inhibition.

Claims 1 and 8-13 were rejected under 35 U.S.C. § 112, first paragraph, because the Examiner believes there is an insufficient written description to show that Applicant was in possession of a "cytotoxic lymphocyte" other than NK or cytotoxic T cell". However, it is well known in the art that the only two "cytotoxic lymphocyte" types are the NK and the cytotoxic T cells. The cytotoxic T-cell is one of three subcategories of T-cells. Helper T-cells and suppressor T-cells, being the other two subcategories of T-cells, are not cytotoxic (page 2, lines 24-29).

In view of the above, the claims are believed fully enabled and Applicants respectfully request withdrawal of all the rejections of Claims 1 and 8-13 under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 112, second paragraph.

The Examiner rejected Claims 1 and 8-13 under 35 U.S.C. § 112, second paragraph, as being indefinite in: a) the recitation of "diphenylionodonium", as now such compound is known to exist; b) the recitation of "the patient" in Claim 1, as this term does not have an antecedent basis in the Claim1; c) the recitation of "said effective amount" in Claims 9 and 10, as it is unclear whether "said effective amount" refers to DPI or ROM inhibitor; d) the recitation of "said cytotoxic lymphocyte stimulatory composition" in Claims 11 and 12, as this term does not have an antecedent basis in Claim 1.

Thus, Applicants have amended the claims as suggested by the Examiner to remove or replace the terms as follows: a) "diphenylionodonium" has been replaced with "diphenylene iodonium"; b) "a subject" in Claim 1 was replaced with "a patient"; c) "said effective amount" in Claims 9 and 10 was described as "of a compound that inhibits the production and release of intercellular reactive oxygen metabolites (ROM)"; d) Claims 11 and 12 were amended to recite "said composition", Claim 1 was amended to recite "a composition", thus creating an antecedent basis for "said composition" in dependent Claims 11 and 12.

In view of the above, the Claims are now believed to be definite and Applicants respectfully request withdrawal of the rejection of Claims 1 and 8-13 under 35 U.S.C. § 112, second paragraph.

CONCLUSION

For all of the above reasons, Applicants respectfully request withdrawal of all rejections under 35 U.S.C. § 112 first and second paragraph, and allowance of the pending application.

Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, amendments to the Claims, the reasons therefor, and arguments in support of the patentability of the pending Claim set are presented above. Any claim amendments which are not specifically discussed in the above remarks are made in order to improve the clarity of claim language, to correct grammatical mistakes or ambiguities, and to otherwise improve the capacity of the Claims to particularly and distinctly point out the invention to those of skill in the art. In light of the above amendments and remarks, reconsideration and withdrawal of the outstanding rejections is respectfully requested. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is invited to initiate the same with the undersigned.

Please charge any additional fees or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 22 APR 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification

Page 7, beginning at line 9 and ending at line 12

In one embodiment the invention relates to a method comprising identifying a patient in need of enhanced cytotoxic lymphocyte activity, and administering to the patient an amount of **[dipenylionodonium]** diphenylene iodonium (DPI) effective to activate and protect cytotoxic lymphocyte function in the presence of MO.

Page 12, beginning at line 28 and ending at line 30

Examples of suitable compounds include **[dipenylionodonium]** diphenylene iodonium (DPI), histamine, compounds with a chemical structure resembling that of histamine or serotonin, yet do not negatively affect H_2-receptor activities.

In the Claims:

Claim 1 has been amended as follows:

1. **(Amended)** A method for activating and protecting cytotoxic lymphocytes in the presence of monocytes (MO), comprising:

identifying a **[subject]** patient in need of enhanced cytotoxic lymphocyte activity; and

administering to the patient a composition comprising an amount of **[diphenylionodonium]** diphelylene iodonium (DPI), effective to activate and protect cytotoxic lymphocyte function in the presence of MO.

9. **(Amended)** The method of Claim 8, wherein said effective amount of a compound that inhibits the production and release of intercellular reactive oxygen metabolites (ROM) is between about 0.05 mg and about 50 mg per dose.

10. **(Amended)** The method of Claim 8, wherein said effective amount of a compound that inhibits the production and release of intercellular reactive oxygen metabolites (ROM) is between about 1 microgram/kg and about 100 **[μg]**microgram/kg of patient weight per dose.

11. **(Amended)** The method of Claim 1, wherein the administration of said **[cytotoxic lymphocyte stimulatory]** composition and said effective amount of a compound that inhibits the production or release of intercellular reactive oxygen metabolites (ROM) is performed within 1 hour.

12. **(Amended)** The method of Claim 1, wherein the administration of said **[cytotoxic lymphocyte stimulatory]** composition and said effective amount of a compound that inhibits the

production or release of intercellular reactive oxygen metabolites (ROM) is performed within 24 hours.

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